REMARKS

In response to an Amendment filed on May 17, 2007, Applicants received a Notice of Non-Compliant Amendment indicating that the claim amendments changed the claims to methods that cover non-elected subject matter. For that reason the Amendment was not entered. The claims have now been changed to composition claims.

Claims 1-3 and 6-8 are pending in the application. Claims 4-5 and 9-32 have been withdrawn without prejudice to Applicants' right to prosecute them in one or more divisional applications. Claim 1 has been amended and is now directed to a composition comprising a substance that prevents or treats epithelial tissue damage, comprising a polynucleotide antisense to a sequence comprising the glucosylceramide synthase gene and/or the glucosylceramide synthase mRNA. It is believed that no new matter has been added to the claims as no limitations not previously found in one or another of the claims has been added. Nevertheless, support for the claims as amended can be found in the specification at page 10, lines 13-24; for example. Claim 6 has been amended and is now directed to a pharmaceutical composition for preventing or treating epithelial tissue damage. In addition, to the passage just recited, additional support for Claim 6 can be found at page 12, line 25 – page 13, line 21, for example. It is believed that no new matter has been added by way of amendment.

Claim 3 has been amended to recite structural limitations that reflect a reduced level of translation product for the CD_{1d} gene as in the original claim. It is believed that no new matter has been added by this amendment. Claim 8 is amended in a similar manner.

The specification has been amended to include sequence identifiers for the recited nucleotide sequences. The figure on page 36 has been denoted as such and a new description has been included in the Brief Description of Figures. Table numbers have been assigned to the tables on pages 30, 35 and 37-38.

Claims 1 and 6 have been amended to place them in conformity with the restriction requirement.

Claims 1-3 and 6-8 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to meet the written description requirement. The Office action took the position that the application must contain a number of polynucleotide substances to provide evidence of possession of the

invention. Applicants request that this rejection be reconsidered and withdrawn for the following reasons. Of the rejected claims only Claims 1 and 6 are independent.

Applicants submit that oligonucleotide design for RNAi knockouts and for antisense technology is well established. This is evidenced by the numerous websites on the internet that are available to help select suitable oligonucleotides. It is well known in the art that many many oligonucleotides are available for both RNAi and antisense strategies. A sampling of web-based oligonucleotide design sites is provided below:

- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&list_uids=15215365&cmd=Retrieve&indexed=google
    - Nucleic Acids Res. 2004 Jul 1;32(Web Server issue):W130-4.
- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?itool=abstractplus&db=pubmed&cmd=Retrieve&dopt=abstractplus&list_uids=16722778
    - Appl Bioinformatics. 2006;5(2):121-
- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?itool=abstractplus&db=pubmed&cmd=Retrieve&dopt=abstractplus&list_uids=15215366
    - Nucleic Acids Res. 2004 Jul 1;32(Web Server issue):W135-41.

In fact, oligonucleotide manufacturers include such programs on their websites and guarantee that oligonucleotide sets ordered from their sites will function. See for example the website for oligonucleotide design at Integrated DNA Technologies, Inc.:

- http://www.idtdna.com/SciTools/SciTools.aspx

This website includes design programs for RNAi and antisense oligonucleotides, which is an even a more established technology.

As can be seen from a review of these sites, all that is required for the design of such oligonucleotides is knowledge of the sequence of a gene or RNA transcript. Using websites such as this, a researcher can simply enter the gene or mRNA sequence information onto the site in order to obtain a number of oligonucleotides that will work for either antisense or RNAi knockout strategies. This entire process occurs within minutes on the website and if that researcher then orders several of those oligonucleotides the researcher will have the oligonucleotides in a short period of time. This aspect requires little in the way of

experimentation. The art is well enough advanced that it is a virtual certainty that one of skill will find a number of oligonucleotides that will work to reduce expression of a target gene.

It is well established that the written description requirement does not require disclosure of methods or techniques that are well known in the art and it goes without saying that the design and manufacture of RNAi or antisense oligonucleotides which can be carried out on publicly available websites within a day by people having less than ordinary skill in the art is certainly well known in the art. Applicants submit that the present application has disclosed all that is necessary to satisfy the written description requirement and respectfully request that the rejection be withdrawn.

Claims 2-3 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. With respect to Claim 2, the phrase "reducing at least one of the transcription and translation of the CD_{1d} gene" was considered indefinite because they reflect processes rather than products. Claim 2 has been amended to refer to a composition, namely a cell, with a lower amount of the translation product. With respect to Claim 3, the list of the sources of compounds was considered inappropriate. While it is submitted the RNAi oligonucleotides were first discovered in plants and in plant material and has since been shown to occur in many other organisms and contexts, Claim 3 has been amended to specifically refer to RNAi oligonucleotides in order to advance prosecution of this application.

The Office action objected to Claim 6 on the basis that it was a duplicate of Claim 1. Claim 6 now refers to a pharmaceutical composition and is distinct from the composition of Claim 1.

Claims 1, 3, and 6 stand rejected under 35 U.S.C. § 102(a) as anticipated by *Di Sano* as evidenced by *Nieda* and *Balreira*. The Office action took the position that *Di Sano* disclosed a glucosylceramide synthase antisense vector that downregulates glucosylceramide synthase activity. Applicants respectfully request that the rejection be withdrawn for the following reasons. *Di Sano* fails to disclose or suggest the use of a polynucleotide that is antisense to an mRNA sequence comprising the glucosylceramide synthase gene and/or the glucosylceramide synthase and that can prevent or treat epithelial tissue damage. Thus, independent Claims 1 and 6 are distinct from *Di Sano* and are not made obvious by *Di Sano*. Claim 3, which depends from Claim 1, is patentable for at least the same reasons.

Claims 1, 3, and 6 stand rejected under 35 U.S.C. § 102(a) as anticipated by *Deng* as evidenced by *Nieda* and *Balreira*. The Office action took the position that *Deng* disclosed a glucosylceramide synthase antisense vector that downregulates glucosylceramide synthase activity when transfected into mammalian cells. Applicants respectfully request that the rejection be withdrawn for the following reasons. *Deng* fails to disclose or suggest the use of a polynucleotide that is antisense to an mRNA sequence comprising the glucosylceramide synthase gene and/or the glucosylceramide synthase and that can prevent or treat epithelial tissue damage. Thus, independent Claims 1 and 6 are distinct from *Deng* and are not made obvious by *Deng*. Claim 3, which depends from Claim 1, is patentable for at least the same reasons.

Claims 1, 3, and 6 stand rejected under 35 U.S.C. §102(a) as anticipated by *Liu*. The Office action took the position that *Liu* disclosed a glucosylceramide synthase antisense vector that downregulates glucosylceramide synthase activity when transfected into mammalian cells. Applicants respectfully request that the rejection be withdrawn for the following reasons. *Liu* fails to disclose or suggest the use of a polynucleotide that is antisense to an mRNA sequence comprising the glucosylceramide synthase gene and/or the glucosylceramide synthase and that can prevent or treat epithelial tissue damage. Thus, independent Claims 1 and 6 are distinct from *Liu* and are not made obvious by *Liu*. Claim 3, which depends from Claim 1, is patentable for at least the same reasons.

Applicants submit that they have made an earnest effort to place the application in allowable form and request that the amendments be entered and considered and that the application be passed to issue. The Commissioner is hereby authorized to charge deposit account 02-1818 for any fees which are due and owing.

Respectfully submitted,
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